

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE



Applicant : David A. Brown, Alexander A. Khorlin, Krystyna Lesiak
and Wu Yun Ren
Serial No. : 10/667,630
Filed : September 22, 2003
Inventor :
Title : DERMATOLOGICAL COMPOSITIONS AND
METHODS

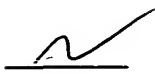
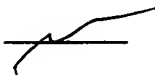
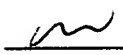

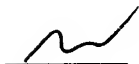


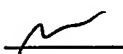


SUPPLEMENTAL MODIFIED 1449 FORMU.S. PATENT DOCUMENTS

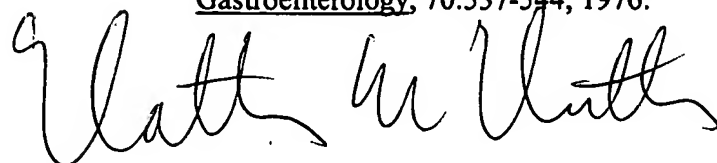
<u>Examiner Initial</u>	<u>Document Number</u>	<u>Issue Date</u>	<u>Name</u>
<u>[Signature]</u>	99. 5,190,978	3/1993	Nakamura et al.
<u>[Signature]</u>	100. 5,525,635	6/1996	Moberg

OTHER ART

<u>Examiner Initial</u>	
<u>[Signature]</u>	101. Krieger, H. "Arzneimittelforschung an Norbornan-Derivaten 2. Mitteilung," ARZNEIMITTEL-FORSCHUNG, vol. 18, no. 3 1968, pages 324-330, XP009020785, with attached English translation of Section 8.
<u>[Signature]</u>	102. Suematsu et al., "Gaseous monoxides: a new class of microvascular regulator in the liver," <u>Cardiovascular Research</u> , 32: 679-686, 1996.
<u>[Signature]</u>	103. Anwer et al., "Essential Role of Sodium and Chloride for Theophylline-Induced Choleresis in the Isolated Perfused Rat Liver," <u>Proceedings of the Society for Experimental Biology and Medicine</u> , 176:70-76, 1984.

3-05

-  104. Barnhart et al., "Characteristics Common to Choleretic Increments of Bile Induced by Theophylline, Glucagon and SQ-20009 in the dog," Proceedings of the Society for Experimental Biology and Medicine, 150:591-596, 1975.
-  105. Barrera et al., "Effect of Epomediol on the ATPase and Adenylate Cyclase Activities in Plasmamembranes Isolated from Rat Liver," Pharmacological Research Communications, 16:1133-1140, 1984.
-  106. Cho, Won Kyoo, "Role of the Neuropeptide, Bombesin, in Bile Secretion," Yale Journal of Biology and Medicine, 70:409-416, 1997.
-  107. Francis et al., "cAMP stimulates the secretory and proliferative capacity of the rat intrahepatic biliary epithelium through changes in the PKA/Src/MEK/ERK1/2 pathway," Journal of Hepatology, 41:528-537, 2004.
-  108. Kaminski et al., "The Effects of Prostacyclin on Canine Hepatic Bile Flow," Hepatology, 4:644-650, 1984.
-  109. Larsen et al., "The effect of glucagons, dibutyrylic cyclic AMP and theophylline on bile production in the cat," Acta Physiol. Scand., 106:23-27, 1979.
-  110. Lenzen et al., "Secretin stimulates bile ductular secretory activity through the cAMP system," Amer. J. Physiol., 263:G527-532, 1992.
-  111. Lenzen et al., "Glucagon induces biliary protein excretion in guinea pigs," Amer. J. Physiol., 264:G961-G966, 1993.
-  112. LeSage et al., "α-1 Adrenergic Receptor Agonists Modulate Ductal Secretion of BDL Rats via Ca²⁺- and PKC-Dependent Stimulation of cAMP," Hepatology, 40:1116-1127, 2004.
-  113. Levine et al., "Cyclic AMP in Secretin Choleresis: Evidence for a regulatory role in man and baboons but not in dogs," Gastroenterology, 70:537-544, 1976.

 3-05

114. McGill, et al., "Secretin activates C1-channels in bile duct epithelial cells through a cAMP-dependent mechanism," Amer. J. Physiol., 266:G731-G736, 1994.

115. Myers et al., "cGMP stimulates bile acid-independent bile formation and biliary bicarbonate excretion," Amer. J. Physiol., 270:G418-G424, 1996.

116. St-Pierre et al., "Stimulation of Bile Acid Independent Bile Flow with Bromo-Cyclic Guanosine Monophosphate," Hepatology, 24:1487-1491, 1996.

117. Taniai et al., "Endothelin B Receptor-Mediated Protection Against Anoxia-Reoxygenation Injury in Perfused Rat Liver: Nitric Oxide-Dependent and -Independent Mechanisms," Hepatology, 33:894-901, 2001.

118. Trauner et al., "Nitric Oxide Donors Stimulate Bile Flow and Glutathione Disulfide Excretion Independent of Guanosine 3', 5'-Cyclic Monophosphate in the Isolated Perfused Rat Liver," Hepatology, 25:263-269, 1997.

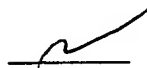
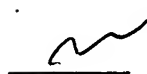

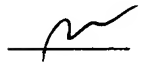
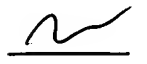

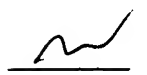

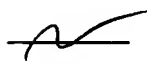

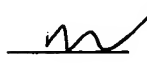
119. Trauner et al., "Nitric Oxide and Guanosine 3', 5'-Cyclic Monophosphate Stimulate Bile Secretion in Isolated Rat Hepatocyte Couplets, But Not in Isolated Bile Duct Units," Hepatology, 28:1621-1628, 1998.

120. Adnot et al., "Pulmonary hypertension: NO therapy?," Thorax, 1996, 51:762-764.

121. Andersson and Stief, "Neurotransmission and the contraction and relaxation of penile erectile tissues," 1997, World J. Urol. 15:14-20.

122. Andersson, K.-E., "Neurotransmitters and neuroreceptors in the lower urinary tract," Curr. Opin. Obstet. Gynecol., 1996, 8:361-365.

123. Baron, A., "Insulin and the Vasculature--Old Actors, New Roles," J. Investig. Med., 1996, 44:406-412.

-  124. Brann et al., "Gaseous Transmitters and Neuroendocrine Regulation," Neuroendocrinology, 1997, 65:385-395.
-  125. Carter et al., "Nitric oxide production is intensely and persistently increased in tissue by thermal injury," Biochem. J., 1994, 304(Pt 1):201-04.
-  126. Cooke and Dzau, "Nitric Oxide Synthase: Role in the Genesis of Vascular Disease," Annu. Ref. Med., 48:489-509, 1997.
-  127. Dawson et al., "Nitric Oxide Actions in Neurochemistry," Neurochem. Int., 1996, 29:97-110.
-  128. Gorfine, S., "Treatment of Benign Anal Disease with Topical Nitroglycerin," Dis. Colon Rectum, 1995, 38:453-456.
-  129. Kone, et al., "Biosynthesis and homeostatic roles of nitric oxide in the normal kidney," Am. J. Physiol., 1997, 10:F561-578.
-  130. Lahera, et al., "Nitric Oxide, the Kidney, and Hypertension," , Am. J. Hypertens. 10:129-140, 1997.
-  131. Marriott and Higenbottam, "The role of nitric oxide in respiratory disease," 1997, Schweiz Med. Wochenschr. 127:709-714 (abstract).
-  132. Mashimo et al., "Effects of Vasodilators Guanethidine, Nicardipine, Nitroglycerin, and Prostaglandin E₁ on Primary Afferent Nociceptors in Humans," J. Clin. Pharmacol., 1997, 37:330-335.
-  133. Murrell et al., "Modulation of tendon healing by nitric oxide," Inflamm. Res., 1997, 46:19-27.
-  134. Packard et al., "Pathogenesis of Posttraumatic Headache and Migraine: A Common Headache Pathway?" Headache, 1997, March 37:142-152.

Watt Hi Watt

3-05

135. Pipili-Synetos et al., "Inhibition of angiogenesis, tumour growth and metastasis by the NO-releasing vasodilators, isosorbide mononitrate and dinitrate," Br. J. Pharmacol., 1995, 116:1829-1834.

136. Rishi et al, " Gastrointestinal Protection by NO from NSAIDs Induced Injury," Indian J. Physiol. Pharmacol., 1996, 40:377-379.

137. Rubbo et al, "Nitric Oxide Regulation of Tissue Free Radical Injury," Chem. Res. Toxicol., 1996, 9:809-820.

138. Samdani et al, "Nitric Oxide Synthase in Models of Focal Ischemia," Stroke, 1997, 28:1283-1288.

139. Schaffer et al., "Nitric Oxide Regulates Wound Healing," J. Surg. Res., 1996, 63:237-240.

140. Thadani, U., "Nitrate Tolerance, Rebound, and their Clinical Relevance in Stable Angina Pectoris, Unstable Angina and Heart Failure," Cardiovasc. Drugs, 1997, 10:735-742.

141. Tooke et al, "Microvascular functional abnormalities in diabetes: the role of the endothelium," Diabetes Res. Clin. Pract., 1996, 31Suppl:S127-S132.






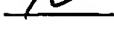
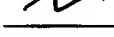
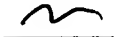



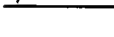
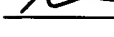
142. Xie et al., "Activation of nitric oxide synthase gene for inhibition of cancer metastasis," J. Leukoc. Biol., 1996, 59:797-803.

3-05

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

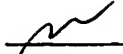



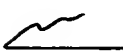



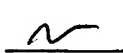





Applicant : David A. Brown, Alexander A. Khorlin, Krystyna Lesiak
and Wu Yun Ren
Serial No. : Not Yet Assigned
Filed : Simultaneously Herewith
For : DERMATOLOGICAL COMPOSITIONS AND
METHODS

MODIFIED 1449 FORMU.S. PATENT DOCUMENTS

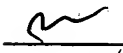



<u>Examiner Initial</u>		<u>Document Number</u>	<u>Issue Date</u>	<u>Name</u>
	1.	3,956,361	5/1976	Stephen
	2.	4,102,995	7/1978	Hebborn
	3.	4,104,203	8/1978	Hall et al.
	4.	4,390,532	6/1983	Stüttgen et al.
	5.	4,528,126	7/1985	Bruns et al.
	6.	4,647,585	3/1987	Loots et al.
	7.	5,041,485	8/1991	Eichenauer et al.
	8.	5,068,453	11/1991	Kuwahara et al.
	9.	5,130,136	7/1992	Shono et al.
	10.	5,232,688	8/1993	Ziegler et al.
	11.	5,302,378	4/1994	Crotty et al.
	12.	5,352,440	10/1994	Gilchrest et al.
	13.	5,414,019	5/1995	Gould et al.

3-05

	14.	5,532,001	7/1996	Gilchrest et al.
	15.	5,554,359	9/1996	Fuller
	16.	5,574,195	11/1996	Chastain et al.
	17.	5,587,402	12/1996	Gould et al.
	18.	5,591,423	1/1997	Fuller
	19.	5,602,184	2/1997	Myers et al.
	20.	5,626,839	5/1997	Scales-Medeiros
	21.	5,698,184	12/1997	Pickart
	22.	5,700,450	12/1997	Gilchrest et al.
	23.	5,990,177	11/1999	Brown
	24.	6,214,888 B1	4/2001	Ren et al.
	25.	6,231,837 B1	5/2001	Stroud et al.
	26.	6,267,948 B1	7/2001	Ren et al.
	27.	6,294,585 B1	9/2001	Brown

FOREIGN PATENT DOCUMENTS

<u>Examiner Initial</u>		<u>Document Number</u>	<u>Date</u>	<u>Country</u>
	28.	0 643 113	3/1995	EP
	29.	1 200 862	8/1970	GB
	30.	WO 87 04617	7/1987	PCT
	31.	WO 89 00853	2/1989	PCT



3-05

<u>✓</u>	32.	WO 96 09810	4/1996	PCT
<u>✓</u>	33.	WO 96/26711	9/1996	PCT
<u>✓</u>	34.	WO 97 03170	1/1997	PCT
<u>✓</u>	35.	WO 97 30692	8/1997	PCT
<u>✓</u>	36.	WO 98 55085	12/1998	PCT
<u>✓</u>	37.	WO 98/11882	3/1998	PCT
<u>✓</u>	38.	WO 99 08654	2/1999	PCT



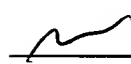
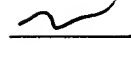
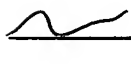
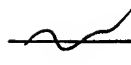
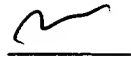
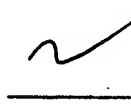
OTHER ART

Examiner
Initial

- | | | |
|----------|-----|---|
| <u>✓</u> | 39. | Abdel-Malek et al., "Mitogenic, Melanogenic, and cAMP Responses of Cultured Neonatal Human Melanocytes to Commonly Used Mitogens," <u>J. Cell. Physiol.</u> , 1992, 150:416-425. |
| <u>✓</u> | 40. | Allan et al., "Topically Applied Diacylglycerols Increase Pigmentation in Guinea Pig Skin," <u>J. Invest. Dermatol.</u> , 1995, 105:687-692. |
| <u>✓</u> | 41. | Barthelman et al., "Inhibitory Effects of Perillyl Alcohol on UVB-induced Murine Skin Cancer and AP-1 Transactivation," <u>Cancer Research</u> , 1998, 58:711-716. |
| <u>✓</u> | 42. | Baudouin et al., "Constitutive Nitric Oxide Synthase Is Present in Normal Human Keratinocytes," <u>J. Invest. Dermatol.</u> , 1996, 106:428-431. |
| <u>✓</u> | 43. | Bradford, M. "A Rapid and Sensitive Method for the Quantitation of Microgram Quantities of Protein Utilizing the Principle of Protein-Dye Binding," <u>Anal. Biochem.</u> , 1967, 72:248-254. |

Clatt G. Huth

3-05

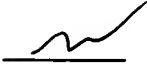


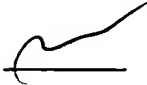






-  44. Brown et al., "Aliphatic and Alicyclic Diols Induce Melanogenesis in Cultured Cells and Guinea Pig Skin," Journal of Investigative Dermatology, 1998, 110:428-437.
-  45. Buchbauer et al., "Norbornanaverbindungen in der pharmazeutischen Forschung," Pharmazie, 1991, 46(Teil 1):88-97, and 46(Teil 2):116-170.
-  46. Buchbauer et al., "Syntheses in the isocamphane series," Chemical Abstracts, Vol. 95, No. 115756e, 1981.
-  47. Carsberg et al., "Ultraviolet radiation-induced melanogenesis in human melanocytes," J. Cell. Sci., 1994, 107:2591-2597.
-  48. Chijiwa et al., "Inhibition of Forskolin-induced Neurite Outgrowth and Protein Phosphorylation by a Newly Synthesized Selective Inhibitor of Cyclic AMP-dependent Protein Kinase, *N*-[2-(*p*-Bromocinnamyl-amino)ethyl]-5-isoquinolinesulfonamide (H-89), of PC12D Pheochromocytoma Cells," J. Biol. Chem., 1990, 265:5267-5272.
-  49. Cieszka et al., "Growth and pigmentation in genetically related Cloudman S91 melanoma cell lines treated with 3-isobutyl-1-methyl-xanthine and β -melanocyte-stimulating hormone," Exp. Dermatol., 1995, 4:192-198.
-  50. Crowell et al., "Chemoprevention of mammary carcinogenesis by hydroxylated derivatives of *d*-limonene," Carcinogenesis, 1992, 13:1261-1264.
-  51. Crowell et al., "Structure-activity relationships among monoterpene inhibitors of protein isoprenylation and cell proliferation," Biochemical Pharmacology, 1994, 47:1405-1415.

Walter M. Luther

3-05

52. Eller et al., "DNA damage enhances melanogenesis," Proc. Natl. Acad. Sci., 1996, 93:1087-1092.
53. Friedmann et al., "Ultraviolet Radiation Directly Induces Pigment Production by Cultured Human Melanocytes," J. Cell. Physiol., 1987, 133:88-94.
54. Fuller et al., "Hormonal Regulation of Melanogenesis in Mouse Melanoma and in Human Melanocytes," Ann. NY Acad. Sci., 1993, 690:302-319.
55. Fuller et al., "Regulation of Tyrosinase in Mouse Melanoma Cells and in Human Melanocytes by PKC and PKA Pathways," Pigment Cell Res., 26th International Pigment Cell Conference Abstracts, 1996, S5:65.
56. Garvey et al., "Potent and Selective Inhibition of Human Nitric Oxide Synthases," J. Biol. Chem., 1994, 269:26669-26676.
57. Gates et al., "Comparison of skin color with melanin content," J. Invest. Dermatol., 1953, 21:339-348.
58. Gilchrest et al., "Mechanisms of Ultraviolet Light-Induced Pigmentation," Photochem. Photobiol., 1996, 63:1-10.
59. Haag et al., "Mammary carcinoma regression induced by perillyl alcohol, a hydroxylated analog of limonene," Cancer Chemotherapy and Pharmacology, 1994, 34:477-483.
60. Hasenfratz "Experience in the treatment of acne vulgaris with the preparation acne-medice," Asthetische Medizin, 15:206-208, 1966.
61. He et al., "Isoprenoids Suppress the Growth of Murine B16 Melanomas In Vitro and In Vivo," J. Nutr., 1997, 127:668-674.

Walter H. Huth 3-05

-  62. Hidaka et al., "Isoquinolinesulfonamides, Novel and Potent Inhibitors of Cyclic Nucleotide Dependent Protein Kinase and Protein Kinase C," Biochemistry, 1984, 23, 5036-5041.
-  63. Introduction to the Cellular and Molecular Biology of Cancer, L. M. Franks and N. Teich, 1987, Oxford University Press.
-  64. Ishida et al., "Biotransformation of terpenoids in mammals," Chemical Abstracts, Volume 93, #89860w, 1980.
-  65. Jager et al., "Investigation of cytotoxic effects of 8 norbornane derivatives on 4 human cancer cell lines using the MTT assay," Pharmazie, 1995, 50:619-621.
-  66. Jara et al., "Assays for Mammalian Tyrosinase: A Comparative Study," Pigment Cell Res., 1988, 1:332-339.
-  67. Jimbow et al., "Biology of Melanocytes," in Dermatology in General Medicine, 4th edition, eds: Fitzpatrick et al., McGraw-Hill, New York, 1993, volume 1, pages 261-289.
-  68. Kamikubo et al., "Preparation of (+)-tricycloen-3-one and its conversion into (+)-epi- β -santalene," Chemical Abstracts, Volume 122, No. 265669u, 1994.
-  69. Karg et al., "Hydrogen Peroxide as a Mediator of Dopac-Induced Effects on Melanoma Cells," J. Invest. Dermatol., 1991, 96:224-227.
-  70. Karg et al., "Hydrogen Peroxide as an Inducer of Elevated Tyrosinase Level in Melanoma Cells," J. Invest. Dermatol., 1993, 100:209S-213S.
-  71. Karg et al., "Stimulation of Tyrosinase by Dihydroxy Phenyl Derivatives," Acta Derm. Venereol., 1989, 69:521-524.

Uatt h Uatt

3-05

72. Karlberg et al., "Hydroperoxides in oxidized *d*-limonene identified as potent contact allergens," Arch. Dermatol. Res., 1994, 286:97-103.

73. Kitahara et al., "Evaluation of Skin Damage of Cyclic Monoterpenes, Percutaneous Absorption Enhancers, by Using Cultured Human Skin Cells," Biol. Pharm. Bull., 1993, 16:912-916.

74. Koval'skaya et al., "Determination of the spatial structure of mono- and bicyclic terpene derivatives on the base of nuclear magnetic resonance spectroscopy data," Chemical Abstracts, Volume 125, No. 276201y, 1996.

75. Kozlov et al, "Camphene in the synthesis oxygen- and nitrogen-containing bicyclic derivatives," Chemical Abstracts, Volume 120, No. 77469p, 1994.

76. Laukharanta et al., "Changes in Three-Dimensional Structure of Cultured S91 Mouse Melanoma Cells Associated with Growth Inhibition and Induction of Melanogenesis by Retinoids," Arch. Dermatol. Res., 1985, 277:147-150.

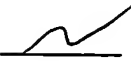
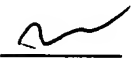

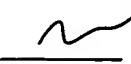
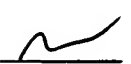


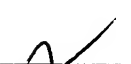

77. McLane et al., "Phosphorylated Isomers of L-dopa Stimulate MSH Binding Capacity and Responsiveness to MSH in Cultured Melanoma Cells," Biochem. Biophys. Res. Commun., 1987, 145:719-725.

78. Merkel, D. "10-Methylenetricyclene," Chemical Abstracts, Volume 66, No. 94723a, 1967.

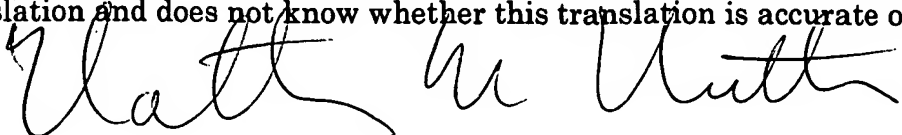
79. Miftakhov et al., "Prostanoids," Chemical Abstracts, Volume 121, No. 157329d, 1994.

80. Miles et al., "Fluorometric Determination of Nitric Oxide," Methods, 1995, 7:40-47.

3-05

-  81. Moshage et al., "Nitrite and Nitrate Determinations in Plasma: A Critical Evaluation," Clin. Chem., 1995, 41:892-896.
-  82. Ohmori et al., "Pharmacological Regulation on Melanogenesis," Nippon Koshohin Kagakkaishi, 1994, 18:215-219. English translation attached¹.
-  83. Orlow et al., "Inhibition of Induced Melanogenesis in Cloudman Melanoma Cells by Four Phenotypic Modifiers," Exp. Cell Res., 1990, 191:209-218.
-  84. Pomerantz, S. H., "The Tyrosine Hydroxylase Activity of Mammalian Tyrosinase," J. Biol. Chem., 1966, 241:161-168.
-  85. Romero et al., "Involvement of Nitric Oxide and Cyclic GMP in Melanogenesis of Human Melanocytes," J. Invest. Dermatol., 1996, 106:886.
-  86. Romero et al., "Retinoic acid as modulator of UVB-induced melanocyte differentiation," J. Cell Sci., 1994, 107:1095-1103, .
-  87. Romero-Graillet et al., "Nitric Oxide Produced by Ultraviolet-irradiated Keratinocytes Stimulates Melanogenesis," J. Clin. Invest., 1997, 99:635-642.
-  88. Romero-Graillet et al., "Ultraviolet B Radiation Acts through the Nitric Oxide and cGMP Signal Transduction Pathway to Stimulate Melanogenesis in Human Melanocytes," J. Biol. Chem. 1996, 271:28052-28056.
-  89. Russin et al., "Inhibition of rat mammary carcinogenesis by monoterpenoids," Carcinogenesis, 1989, 10:2161-2164.

¹ This English translation was provided to the prior assignee of this application by a competitor. Applicant has not made an independent translation and does not know whether this translation is accurate or not.

 3-85

- ✓ 90. Schmidt et al., "Determination of Nitric Oxide via Measurement of Nitrite and Nitrate in Culture Media," 1995, Biochemica 2:22.
- ✓ 91. Shi et al., "Induction of differentiation in neuro-2A cells by the monoterpene perillyl alcohol," Cancer Letters 95, 1995, 1-6.
- ✓ 92. Shoff et al., "Concentration-dependent Increase of Murine P388 and B16 Population Doubling Time by the Acyclic Monoterpene Geraniol," Cancer Research, 1991, 41:37-42
- ✓ 93. Siracký et al., "Relationship between melanogenesis, proliferative activity and response to chemotherapy of human melanoma xenografts," Neoplasia, 1984, 31:545-549, .
- ✓ 94. Southan et al., "Isothioureas: potent inhibitors of nitric oxide synthases with variable isoform selectivity," Br. J. Pharmacol., 1995, 114:510-516.
- ✓ 95. Toullec et al., "The Bisinodylmaleimide GF 109203X is a Potent and Selective Inhibitor of Protein Kinase C," J. Biol. Chem., 1991, 266:15771-15781.
- ✓ 96. Uçar, K., "The effects of histamine H2 receptor antagonists on melanogenesis and cellular proliferation in melanoma cells in culture," Biochem. Biophys. Res. Commun., 1991, 177:545-550 .
- ✓ 97. Uchida et al., "Electrochemical oxidation of polycyclic cyclopropanes and camphene," Chemical Abstracts, Volume 112, No. 198816t, 1990.
- ✓ 98. Wintzen et al., "Proopiomelanocortin, Its Derived Peptides, and the Skin," J. Invest. Dermatol., 1996, 106:3-10.

Walter H. Wintzen 3-05